RESPONSE

Applicants respectfully traverse this rejection. The presently pending claims are patentable over the cited references. The Examiner has failed to establish a *prima facie* case of obviousness against the presently pending claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04-1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new

invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR, supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

A. The teachings of the Primary Larsson et al. reference

The Larsson et al. reference discloses the oxidation of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylthio]-1H-benzimidazole to prepare its sulfoxidized product, (-)- or (S)-pantoprazole, using titanium(IV) isopropoxide, a chiral **titanium** complex, and (-)-diethyl D-tartrate, a chiral auxiliary, in the presence of cumen hydroperoxide(CHP), an oxidizing agent. For instance, Example 23 uses (-)-diethyl D-tartrate as a chiral auxiliary for the preparation of (-)- or (S)-pantoprazole, which is assumed due to the use of a chiral

titanium complex, and uses (+)-diethyl L-tartrate as a chiral auxiliary for the preparation of (+)- or (R)-pantoprazole (see, Example 24).

B. The teachings of the Secondary Bonchio et al. reference

Bonchio et al. disclose that a chiral zirconium complex having a polydentate ligand can be used for the oxidation of aryl alkyl sulfides and dialkyl sulphides with high enantioselectivity, in the presence of cumen hydroperoxide(CHP) as an oxidizing agent. Bonchio et al., however, disclose the zirconium complex as having the **opposite** enantiomeric selection as compared to an analogous titanium complex. In particular, Bonchio et al. disclose that, in a reaction employing the same ligand for the two metals, zirconium and titanium catalysts lead to the preferential formation respectively of (R)-product and (S)-product (see, Bonchio et al., last paragraph of second column and the sentence right above formula (1) of third column). In addition, neither the compound, 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylthio]-1H-benzimidazole for the preparation of (-)-pantoprazole, nor the high optical purity of the product of over 90%, is disclosed in Bonchio et al.

C. No *prima facie* case of obviousness has been established

Based on the divergent teachings of the cited references, the Examiner has clearly failed to establish a *prima facie* case of obviousness.

First, the skilled person learns from Larsson et al. that prior attempts to develop processes for enationselective sulphoxidation proved to be not very useful or successful for substituted benzimidazole compounds (col. 2, line 62 to col. 3, line 17) and only Larsson et al. were able to provide a process for producing single enantiomers of or enantiomerically enriched substituted benzimidazoles. However, Larsson et al. used a chiral titanium catalyst together with an oxidising agent (col. 8, line 1) and further found that the order of addition of each component influences strongly the enantioselectivity of the sulphoxidation (col. 9, lines 56 - 60). Thus, the teachings of Larsson et al. would lead a person of ordinary skill in the art to only pick titanium as the catalyst of choice.

Further, Larsson et al. teach that several additional parameters affect the outcome of the enantioselective synthesis. In particular, Larsson et al. mention the order of addition of the reacting compounds (p 17, line 25 - 28: "By alter the order of addition compared to the processes

disclosed in prior art the enantioselectivity of the oxidation is surprisingly enhanced."), temperature (p 15, lines 18 - 21: "Surprisingly, the process does not require a temperature below -20°C, as described by Kagan and co-workers as essential for good enantioselectivity."), reaction time for the preparation of the chiral catalyst (p 17, line 30 to p 18, line 4: "A prolonged preparation time is a period of time longer that approximately 20 minutes, preferably 1 to 5 hours") or the amount of catalyst used (p 16, lines 6 - 10: "Surprisingly, even very low amounts of complex, such as for instance 0.04 equivalents may be used in the processes according to the present invention with excellent results."). An additional factor influencing the result of the process is whether a base was used or not (col. 9, lines 23 - 55).

Taking this teaching, the person skilled in the art realizes that the compliance with the described parameters is essential for a successful oxidation process, especially if compared with the teaching of the prior art, which also relies on a titanium catalyst. Any deviation from these specifications would end in disadvantageous results of the sulfoxidation reaction, for example requiring additional steps for purification of the final product, i.e. separation of unwanted compounds or need for larger amounts

of reacting compounds. Such measures lead to economical disadvantages, especially when done with larger amount of compounds.

Accordingly, Larsson et al. clearly teach the skilled person that the process parameters, in particular the actual compounds used in the sulphoxidation process, play a crucial role in order to obtain enantiomers of or enantiomerically enriched substituted benzimidazole compounds and specifically enantiomeric pantoprazole. A skilled person would clearly recognize that any changes to the teachings of Larsson et al. will lead to less satisfactory results.

The teachings of the secondary Bonchio et al. reference do not remedy the deficient teachings of the Larsson et al. reference. In fact, Bonchio et al. teach away from the teachings of the Larsson et al. reference and, as such, no person of ordinary skill in the art would be motivated to combine the Larsson et al. and Bonchio et al. references.

Bonchio et al. describes a process for stereoselective sulfoxidation by use of a chiral zirconium (IV) catalyst. The document discloses that good results with respect to the enantioselectivity for a number of exemplary alkyl aryl sulfides can be obtained. But the document emphasisizes

that only a very small number of examples using a zirconium catalyst were known and the disclosed information are first results of ongoing investigations (page 1326, left column, third full paragraph and page 1327, last sentence of paragraph bridging right and left column) and even more, these reactions usually provided results being worse than the comparable titanium catalysts (p 1326, left column, lines 12ff). There are no secured indications given whether the results are transferable to other type of compounds such as the presently claimed (-)-pantoprazole.

Further, the skilled person will realize quite easily that the examples described in Bonchio et al. show alkyl aryl sulfides with structurally simple alkyl (methyl, *i*-propyl, *t*- or *n*-butyl) or aryl (phenyl, *para*-methyl-, *para*-chloro- or *para*-methoxylphenyl, naphthyl) substituents. These substituents are structurally much different than the substituted benzimidazole- or substituted 2-methylpyridinyl-substituent of (-)-pantoprazole.

Further, although the document describes good results for the enantiomeric excess of the tested compounds, it is also clearly visible to the skilled person from table 3 (page 1328, left column) that the reaction is not really selective with respect to the end products. The analysis of the reaction products of the tested alkyl aryl sulfides

shows mostly a much higher amount of sulphon than sulphoxide, for some examples more than the double amount of sulphon than of sulphoxide - and a sulphon is not the compound the skilled person intends to obtain from the described process! Although the document describes by way of an example (methyl-*p*-tolylsulfide) how the amount of the sulphon can be reduced, it simultaneously teaches that this is achieved with a reduction of the conversion rate of the starting compound, extreme long reaction time and - even worse - a concomitant loss of enantioselectivity for the final product!! (page 1327, left column, table 1, entries 4 to 7). These are clearly not the conditions the skilled person would look for.

Also, with respect to the comparability of both catalyst metals, it is made very clear to the skilled person that the results of the Ti catalyst are not identical or transferable to the Zr catalyst (p 1327, left column: Results and Discussion).

Although a Zr catalyst was prepared according to the identical process as described for the Ti catalyst, the Zr catalyst is shown to be clearly less effective than the Ti catalyst:

> The Zr(IV) catalyst 5b was first prepared in situ under anhydrous conditions (Scheme2, path a), by reacting Zr-(*n*-BuO)$_4$ with 1b using the same protocol developed for the analogous Ti(IV)

> system 2b (Scheme 1, path a). System 5b showed little catalytic activity. Oxidation of the model substrate methyl *p*-tolylsulfide 7 (..) by CHP (..) in the presence of 5b (..) proceeded slowly (10% conversion of the oxidant in 4h), affording (*R*)-methyl-*p*-tolylsulfoxide 8 in low enantiomeric excesses (23%)").

Accordingly, the disclosure of Bronchio et al. may be summarized by a skilled person in such a way that a Zr catalyst shows significant differences as compared to an analogous Ti catalyst and that based on this quite new knowledge a transfer of experience from the field of Ti catalysts to the field of Zr catalysts can not be made. It is therefore very unexpected that the use of a chiral Zr catalyst as presently claimed, would result in a high conversion rate and a high enantioselectivity by concurrently low amounts of sulfone by-products being formed. It is clear that the ordinary skilled artisan would not recognize from the teachings contained in the Bonchio et al. disclosure that simply exchanging the catalyst metal would produce a high conversion rate and a high enantioselectivity while producing low amounts of sulfone by-products.

Accordingly, there is clearly no motivation to combine the Larsson et al. reference with the Bonchio et al. reference and no prima facie case of obviousness has been demonstrated by the Examiner.

As such, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

2. Provisional Rejection of claims 1-6, 10-15 and 21-28 under the doctrine of obviousness type double patenting

The Official Action states that claims 1-6, 10-15 and 21-28 are provisionally rejected under the doctrine of obviousness-type double patenting over claims 1-22 of co-pending application serial number 10/536,766.

Applicants traverse this rejection. Applicants respectfully submit that this is a provisional rejection and must be withdrawn as the presently pending claims are now in condition for allowance.

Accordingly, applicants respectfully request that the Examiner withdraw this provisional rejection so that this application may proceed to grant.

CONCLUSION

Based upon the above amendment and remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the pending rejections and allow all pending claims of this application. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

If the Examiner has any questions or wishes to discuss this matter, the Examiner is welcomed to telephone the undersigned attorney.

Respectfully submitted,

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